CODING FORM FOR SRC INDEXING REVISED 10/15/86

Microfiche No.

OTS0515198

New Doc I.D

86-870000671

Old Doc I.D.

Date Produced

10/03/83

Date Recieved

7/25/87

TSCA section

8D

Submitting Organization

INTL ISOCYANATE INST

Contractor

HAZLETON LABS EUROPE

Document Title

SUMMARY REPORT - CHRONIC (2 YEAR) TOXICITY AND CARCINOGENICITY INHALATION STUDY OF TOLUENE DIISOCYANATE IN MICE

Chemical Category

TOLUENE DIISOCYANATE (1321-38-6)

THE TOXICITY AND CARCINOGENICITY OF TOLUENE DIISOCYANATE VAPOUR WHEN ADMINISTERED TO MICE OVER A PERIOD OF APPROXIMATELY 2 YEARS

SUMMARY REPORT

Report for:

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Report No:

2519-484/2

1. SUMMARY

1.1 A long term study of the inhalation toxicity and carcinogenicity to mice of Toluene diisocyanate vapour (TDI) has been completed. The animals were exposed 6 hours per day, 5 days a week for approximately 2 years.

1.2 In an earlier study (HLE project number 484/1) a laboratory system had been developed for the generation and analysis of TDI vapour in air.

1.3 The distribution of TDI vapour in the exposure chambers was monitored before the start of the animal phase of the study and after 6 and 12 months of exposure. On all occasions an acceptable agreement between target and monitored concentrations was found.

1.4 Three hundred and sixty male and 360 female mice of the CD1 strain were utilised for exposure to TDI vapour. Three groups: control, 0.05 ppm TDI and 0.15 ppm TDI each consisting of 120 males and 120 females were used. In addition 5 males and 5 females were added to each group for cytogenicity studies.

1.5 Before the start of animal exposures both microbiological and histopathological screens were carried out on both a sample of animals as supplied and some of the dams from which they were derived. No adverse findings were detected.

1.6 Throughout the study, both temperature and humidity within

the exposure room and the individual exposure chambers maintained a close adherence to the values stipulated in the protocol. Any deviations which did occur were fully documented.

1.7 The weekly mean TDI concentrations in the control chamber were consistently less than 0.001 ppm throughout the study.

For the low dose chamber the concentrations were within 4% of the target concentration on all but 3 occasions throughout the total duration of the study. For the high dose chamber the concentrations were within 1.3% of the target concentration on all but 6 occasions throughout the total duration of the study.

1.8 A number of common clinical signs associated with the stress of the exposure procedure were recorded; these included lumped/kinked tails, generalised staining, sore paws, torn ears and epilation.

From week 65 to termination a treatment-related increase in the incidence of swollen abdomens and opaque watery eyes was detected.

1.9 Using statistical analyses it was established that males receiving 0.15 ppm TDI were less likely to develop a palpable mass before study termination than were control animals and those exposed to 0.05 ppm TDI. This finding was not thought to have any biological significance. For female animals no differences between control and treated animals were apparent.

1.10 The number of animals surviving at termination was as follows:

	Males	Females
Controls	25	40
Low dose	34	27
High dose	34	29

Statistical analysis indicated that there was no overall significant difference between the survival patterns of the control, low dose and high dose male groups. For female animals however, there was a statistically significant difference in the survival patterns of the control, low dose and high dose groups. Furthermore this difference in survival showed a trend for increasing mortality with increasing dose level.

1.11 The statistical analyses of body weight gains showed that for males and females receiving 0.15 ppm TDI there was a consistent reduction in weight gain compared with the controls. Males and females receiving 0.05 ppm TDI had weight gains generally similar to those of control animals.

1.12 There were no changes in haematological, blood chemical or urine analysis parameters of the treated mice which could be unequivocally attributed to exposure to the test article.

1.13 The results of the cytogenicity study indicated that there

were no differences between treated and control animals.

1.14 The statistical analysis of both absolute organ weights and organ/brain weight ratios for animals killed after 26, 52, 78 weeks and terminally revealed a number of statistically significant differences between treated animals and controls. None of the differences observed were considered to be of toxicological importance.

1.13 Exposure to TDI produced upper respiratory tract lesions in the majority of mice, and morbidity and mortality due to rhinitis at both dose levels. The rhinitis was accompanied to a lesser extent by lesions in the lower respiratory tract and cornea.

There was no evidence of any oncogenic effect due to exposure to TDI.

1.16 Dose-related trends for necrotic rhinitis (males and females), interstitial pneumonitis (males and females), bronchitis (males and females), and multiple pulmonary adenomas (males only) were identified.

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Data produced 11 (Month) 14 (Day) 88 (Year) Barbara Smith Camera Operator

Place Syracuse (City) New York (State)

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